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EXAMINER

FOSTER, CHRISTINE E

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 03/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/661,790

Applicant(s)

YAMAZAKI ET AL.

Examiner

Christine Foster

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 10 and 26-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 10 and 26-41 is/are rejected.
- 7) ☒ Claim(s) 1, 10 and 40 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 1/20/06 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment, filed 1/20/06, is acknowledged and has been entered.

Claims 8-9 and 11-25 have been canceled.

Claims 1-4, 10, 26-29, and 40 have been amended.

Election/Restrictions

2. Claims 26-33, 37-39, and 41 were cancelled in the amendment filed 7/29/05. However, the amendment filed 1/20/06 presents these claims using the status identifiers 'currently amended' (claims 26-29) or 'original' (claims 30-33, 37-39, and 41).

Claims 26-33, 37-39, and 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/29/05.

Claims 1-7, 10, 34-36, and 40 are currently under examination.

Rejections Withdrawn

The objection to the oath/declaration is withdrawn in light of the filing of a new declaration on 2/2/06.

The objections to the Drawings are withdrawn in light of filing of Replacement Sheets for Figures 1, 3, and 5 on 1/20/06.

The objection to claim 14 is withdrawn in light of the claim's cancellation.

The rejection of claim 1 under 35 USC 112, 2nd paragraph for being unclear regarding the plurality of lipid bilayer expanses recited in lines 7-8 (see item 4 of the previous Office action) is withdrawn upon reconsideration by the Examiner, and has instead been addressed as an objection to the claim (see below). The claim remains rejected under 35 USC 112, 2nd paragraph for the reasons set forth below.

The rejections of claims 9-13 under 35 USC 112, 2nd paragraph are withdrawn in light of Applicant's amendments removing reference to "acyl chain mobility" from the claims.

The rejections of claims 17-18 under 35 USC 112, 2nd paragraph are withdrawn in light of the cancellation of these claims.

The rejection of claim 36 under 35 USC 112, 2nd paragraph for recitation of the term "phantom cell" is withdrawn in response to Applicant's arguments (p. 15) and upon further reconsideration by the Examiner.

The rejection of claim 40 under 35 USC 112, 2nd paragraph is withdrawn upon further reconsideration by the Examiner.

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The rejections of claims 1-2, 4-8, 14-15, 19-20, and 34-36 under 35 USC 102(b) as being anticipated by Boxer et al. are withdrawn in response to Applicant's amendments to claim 1 to recite the step of evaluating the fluidity of the lipid bilayer expanse(s). However, the reference has been applied in the rejections under 35 USC 103(a) below.

Information Disclosure Statement

3. Applicant is reminded that abstracts and other references submitted for consideration by the examiner should be submitted in accordance with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.

The references submitted with the amendment and as the reference submitted as part of the above declaration do not constitute a proper information disclosure statement because they were not accompanied by a list of the references. The references have been placed in the application file, but the information referred to therein has not been considered unless otherwise indicated.

4. The reference by Wagner and Tamm referred to in Applicant's response at p. 14 is not a proper information disclosure statement in compliance with 37 CFR 1.98(a)(2), which requires a

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legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

Claim 1 is objected to because it is unclear whether lines 7-8, which refer to a plurality of lipid bilayer expanses, are intended to be a method step or are reciting further components of the surface detector array device of line 3. The claim punctuation appears to indicate that lines 7-8 follow under the heading of the claim's preamble ("A method...comprising:") rather than under the heading of "...said device comprising...". It is suggested that the claim be reworded in order to clearly indicate that the device comprises both (1) substrate and (2) plurality of lipid bilayer expanses.

Claim 1 is objected to because the last two lines of the claim refer to "the fluidity", yet the previous reference to fluidity in the claim refers to "**membrane** fluidity". It is suggested that the claim refer to "the membrane fluidity" in order to maintain consistency with the prior reference in the claim.

Claim 10 is objected to for grammatical reasons. The amended claim recites "...wherein said evaluating the membrane fluidity comprises...". It is suggested that the word "said" be removed to read --wherein evaluating the membrane fluidity comprises--. Alternatively, the claim may recite --wherein said **evaluation of** membrane fluidity comprises--.

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Claim 40 is objected to for grammatical reasons because the claim is a run-on sentence. It is suggested that “**said method** further comprising” be replaced with --**and** further comprising--.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 4-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Amended claim 4 recites that the lipid bilayer-associated component is a label. The claims previously recited that the plurality of lipid bilayer expanses **comprises** a label. Because independent claim 1 has also been amended to recite that the test agent binds to the lipid bilayer-associated component, claim 4 now recites that the test agent specifically binds to a label, which represents a departure from the specification and claims as originally filed. The specification indicates that labels are *attached to or incorporated within* a lipid bilayer-associated component (p. 14, lines 19-23). In other words, the specification indicates that the test agent binds directly to the lipid bilayer-associated component, which may be attached to a label. Support could not be found in the specification for a situation in which the test agent specifically binds directly to a label, and Applicant did not indicate where such support may be found.

In addition, claim 5 recites that the label is attached to a “target membrane component”. The specification indicates that this term has the same meaning as a “lipid bilayer-associated component” (p. 6, lines 32-33). Because claim 4 has been amended to recite that the lipid bilayer-associated component is a label, claim 5 now appears to recite that the lipid bilayer-associated component/label is attached to itself (see rejection under 112, 2nd paragraph below). In claim 6, the recited limitation that the label is attached to a background membrane component would require that the target membrane component (the lipid bilayer-associated component) and the background membrane component be attached to each other. No support could be found in the specification for such a situation.

6. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack a written description for the following reasons. Independent claim 1 is drawn to a method for assaying an interaction between a test agent and a lipid bilayer-associated component, where a physical property of one or more lipid bilayer expanses is evaluated during the method. The claims are therefore drawn to a genus of test agents and lipid bilayer-associated components. The claims also encompass detection of the interaction by evaluating the membrane fluidity of the bilayer, although other types of detection are also encompassed as there is no recited correlation between evaluation and detection in the claim.

The claimed genus of test agents includes small molecules, cell surfaces, vesicles, and biomolecules, and other agents (see also claims 34-36). The claimed genus of lipid bilayer-associated components that interact with test agents include proteins, nucleic acids, glycolipids, lipopolysaccharide, sterols, lipid-linked molecules, fatty acids, and endotoxins (claims 2-3). However, the claimed genera of test agents and lipid bilayer-associated components have no disclosed partial structure, shared physical and/or chemical properties, or shared functional or other identifying characteristics. In particular, there is no disclosure of that the genera of test agents/lipid bilayer-associated components are known to affect physical properties of the bilayer upon interaction. With regard to claims 34-36, there is no disclosure that small molecules, proteins other than cholera toxin subunit B, cells, vesicles, phantom cells, liposomes, giant vesicles, lipid-covered glass beads, or components thereof are known to affect the membrane fluidity of the bilayer upon interaction.

The specification discloses only a single test agent (cholera toxin subunit B) that is capable, upon interaction with a lipid bilayer-associated component (ganglioside GM1), of changing the membrane fluidity of the bilayer (see p. 23, lines 9-12 in particular). There are no working examples of other test agent-component pairs.

With regard to claim 3, there is no written description of a method for detecting the interaction of a test agent with bilayer-associated bacterial endotoxin by evaluating a physical property of the bilayer, as in claim 3. In Examples 3-4, 6 and in Figures 5C, 5D, 8, and 9, the endotoxin cholera toxin subunit B is the **test agent**, and not the **lipid bilayer-associated component** (see p. 25, lines 17-19 in particular). Example 5 discloses endotoxins as lipid bilayer-associated components in which test agents are screened for interaction (p. 31, line 23 to

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p. 32, line 2). However, this example appears to be prophetic, and there is no disclosure that the interaction of such agents with bilayer-associated endotoxins affects membrane fluidity of the bilayer.

7. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assaying an interaction between test agents that are bacterial endotoxins such as cholera toxin and lipid bilayer-associated components that are endotoxin receptors such as ganglioside GM1, does not reasonably provide enablement for assaying an interaction with other test agent-component pairs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Independent claim 1 recites a method for assaying an interaction between a test agent and a lipid bilayer-associated component. The lipid bilayer-associated component is associated with a substrate-supported lipid bilayer that is provided as part of a surface detector array device, which comprises multiple lipid bilayer expanses that are separated from each other by barrier regions. The method for assaying an interaction includes the step of contacting the device with the test agent, so as to allow the test agent to bind to its lipid bilayer-associated ligand. The method also includes the step of evaluating the membrane fluidity of one or more lipid bilayer expanses of the device.

The claims fail to clearly recite that the step of evaluating membrane fluidity is correlated with detection of the interaction between test agent and ligand (i.e., that the interaction is detected by evaluating a decrease in membrane fluidity). See the rejection under 112, 2nd

paragraph below for omission of essential steps. However, the disclosure states that “In accordance with the present invention, binding events are detected through their effects on one or more physical properties of the lipid bilayer, such as membrane fluidity (e.g., p. 14, lines 13-15; p. 26, lines 3-14). Because the claim does not specifically recite a detection step, traditional methods of detecting binding are encompassed by the claim, including secondary screening, detection of radiolabeled components, chemiluminescent detection, and others. The claim also encompasses the disclosed method of detecting binding by evaluating changes in the fluidity of the membrane. Test agents that are encompassed include small molecules, polypeptides, antibodies, biomolecules, cell surfaces, vesicles, and phantom cells, for example (see p. 3, lines 6-12).

The claims are thus broadly drawn to methods of assaying binding or other types of interactions between a large number of possible test agents and lipid bilayer-associated components, where the interaction may be detected by evaluating the membrane fluidity of the bilayer or by other detection methods.

The specification discloses that binding of cholera toxin to lipid bilayer-associated ganglioside GM1 can affect the fluidity of lipid molecules in the neighborhood of the ganglioside (p. 14, line 33 to p. 15, line 4). The specification also provides working examples demonstrating that binding of cholera toxin to membranes presenting GM1 may be detected indirectly by evaluating changes in membrane fluidity (Examples 3-4). The examples evaluate membrane fluidity by FRAP (Example 3) and by electrophoresis (Example 4).

The prior art teaches that the important feature in the interaction of cholera toxin with ganglioside GM1 is *polyvalent binding*, as up to five GM1 receptors can bind to each cholera

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toxin molecule (Song et al., US Patent No. 6,297,059, column 8, lines 32-40 and column 6, lines 6-9). The interaction of cholera toxin with GM1 is therefore able to bring two or more GM1 receptors into close proximity (column 6, lines 1-5), which can be measured by fluorescence self-quenching or FRET (column 5, lines 49-51 and column 7, lines 44-67 in particular).

Therefore, unlike the polyvalent cholera toxin, the binding of other test agents such as small molecules to bilayer-associated ligands would not necessarily have effects on membrane fluidity and other physical properties of the bilayer. In fact, the prior art teaches that some small molecules such as taurine have no effect on membrane fluidity upon interaction with membranes (Moran et al., "Effect of Tocopherol and Taurine on Membrane Fluidity of Retinal Rod Outer Segments," (1987) Exp. Eye Res. 45:769-776, the abstract and p. 775, lines 10-12).

The specification provides no examples of test agents other than cholera toxin that affect membrane fluidity or other physical properties upon binding. There are no working examples of other test agent/bilayer-associated component pairs that demonstrate such effects upon interaction.

The claims also encompass test agents interacting with lipid bilayer-associated integral membrane proteins. The prior art teaches that integral membrane proteins in supported bilayers may often be non-functional, and therefore incapable of interacting with test agents. Boxer et al. teach that:

[I]ntegral membrane proteins are immobile or exhibit severely restriction motion in supported bilayers. It is presumed that this is a result of interactions between the membrane protein and the solid support; there have been relatively few careful studies of the functional consequences of this interaction, but it is generally thought that these interactions will reduce or eliminate protein function.

See Boxer et al., "Molecular transport and organization in supported lipid membranes" (2000) Curr. Opin. Chem. Biol. 4:704-9, p. 705, right column, "Softer surfaces and Tethering," lines 1-9). Boxer et al. further teach that "lipid bilayers and membrane proteins are notoriously difficult to work with" (ibid, p. 704, right column, lines 14-15). The instant specification discloses that "Observations of labeled CTB [cholera toxin subunit B] indicate that it is relatively immobile when bound to supported membranes" (p. 34, lines 21-22). From the above teachings of Boxer et al., this may indicate that CTB is non-functional, and would therefore be incapable of interacting with test agents. This would be of particular relevance to claim 3, in which bacterial endotoxins may be the lipid bilayer-associated component that interacts with test agents. This is contrasted with the examples presented disclosure, in which cholera toxin is the test agent rather than the lipid bilayer-associated component.

More generally, the specification does not provide direction regarding the preservation of function of integral membrane proteins or other lipid bilayer-associated components. There are no working examples of functional lipid bilayer-associated components that interact with test agents, other than ganglioside GM1.

In summary, the prior art establishes that the test agent-component pair of cholera toxin-ganglioside GM1 has important features (such as polyvalency) that allow for detection of interaction by changes in physical properties within the membrane. However, these features are not shared by all test agent-component pairs encompassed by the claims. The prior art also teaches the unpredictability of preparing functional lipid bilayer-associated components such as integral membrane proteins. Therefore, due to the state of the prior art, the lack of direction/guidance presented in the specification regarding detection of interactions by

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evaluation of physical properties where the test agent-component pairs are other than cholera toxin-GM1, the lack of working examples directed to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The preamble of the claim recites “assaying an interaction between a test agent and a lipid bilayer-associated component” (lines 1-2). However, the claim does not set forth steps for assaying or detecting such an interaction (see the previous Office action at item 3).

The claim recites contacting a surface detector array device with a test agent that specifically binds to a lipid bilayer-associated component. The lipid bilayer-associated is associated with lipid bilayer expanses of the device. The claim also recites that the membrane fluidity decreases when the test agent binds to the lipid bilayer-associated component, and includes the step of evaluating the fluidity of the lipid bilayer expanses of the device. The claim fails to recite a detection step—although the specification indicates that the binding of the test agent to the lipid bilayer-associated component can be detected by detecting changes in the

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fluidity of the lipid bilayer expands, this is not recited in the claim. The claim does not recite any correlation between the evaluation of fluidity and the detection of the interaction. Thus, the method steps set forth do not clearly relate back to the method objective recited in the preamble, which is to detect binding between a test agent and a lipid bilayer-associated component.

Alternatively, a correlation step may be added that describes how the results of the detection step (evaluation of fluidity) relate to the binding between the test agent and the component.

10. Claims 4-7 are indefinite because amended claim 4 now recites that the lipid bilayer-associated component is a label. The claims previously recited that the plurality of lipid bilayer expands **comprises** a label (see also rejection under 112, 1st paragraph above). Because claim 1 has also been amended to recite that the test agent binds to the lipid bilayer-associated component, claim 4 now recites that the test agent binds to a label, which is confusing because the specification indicates that labels are *attached to or incorporated within* the lipid bilayer-associated component (p. 14, lines 19-23), i.e. that the test agent binds directly to the lipid bilayer-associated component, which may be attached to a label. The specification does not indicate that the test agent binds directly to the label.

In addition, claim 5 recites that the label is attached to a “target membrane component”. The specification indicates that this term has the same meaning as a “lipid bilayer-associated component” (p. 6, lines 32-33). Yet claim 4, from which claim 5 depends, recites that the lipid bilayer-associated component is a label, giving rise to the circular recitation that the lipid bilayer-associated component/label is attached to itself. In addition, in claim 6, the recited limitation would require that the target membrane component (lipid bilayer-associated component) and the

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background membrane component be attached to each other (see p. 6, lines 32-33 to p. 7, line 2). It is unclear how the label can be the target membrane component and also be attached to a background membrane component since these are distinct species.

For the purposes of examination, claims 4-5 have been interpreted as indicating that the lipid bilayer-associated component **comprises** a label. The lipid bilayer-associated component and the target membrane component have been assumed to refer to the same entity. Claim 6 has been interpreted as indicating that a label is attached to a background membrane component, i.e. to a component other than the lipid bilayer-associated component or target membrane component to which the target agent specifically binds.

11. Claim 36 is rejected for recitation of a "cell-vesicle." The term is not defined in the specification and does not appear to be well known in the art. It is unclear what is meant by the term.

12. The term "giant" in claim 36 (referring to a "giant vesicle") is a relative term that renders the claim indefinite. The term "giant" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 1-2, 4-6, 10, and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al. (US Patent No. 6,228,326; referred to as “Boxer et al.”), or, alternatively, by Boxer et al. (WO 98/23948; referred to as “Boxer ‘98”), which contains the same teachings, in view of Groves et al. (“Micropatterning Fluid Lipid Bilayers on Solid Supports,” (1997) *Science* **275**:651-653).

The column and line numbers discussed below refer to those in Boxer et al., US Patent No. 6,228,326, unless otherwise stated.

Boxer et al. teach a surface detector array device comprising a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier, where the bilayer-compatible surface regions and the bilayer barrier regions are formed of different materials. The surface array detector device also comprises a plurality of lipid bilayer expanses located above the plurality of distinct bilayer-compatible surface regions, wherein the expanses are localized above the surface regions in the absence of covalent linkages to the surfaces and are separated from the surfaces by an aqueous film (column 3, lines 28-40).

Boxer et al. further teach that the device may be used in a method for detecting binding between a test agent and a lipid bilayer-associated component (column 4, lines 25-31 and 41-43; column 12, lines 12-15, 31-33 and 39-42; and column 15, line 65 to column 16, line 7), wherein a bulk aqueous phase comprising the test agent is contacted with the device (column 17, line 65 to column 8, line 5).

In order to detect interaction between the test agent and the lipid bilayer-associated component, a physical property of a lipid bilayer expanse may be evaluated and correlated with binding of the test agent; for example, a change in the transmembrane voltage or current may be

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measured (column 18, lines 5-12) or changes in the bilayer environment surrounding a lipid bilayer-associated receptor in response to binding of a ligand may be detected by SPR (column 16, lines 11-38).

Boxer et al. and Boxer '98 teach evaluation of membrane fluidity by FRAP and by electrophoresis (column 6, lines 18-65; Examples 2-3). However, in Boxer et al. and Boxer '98, evaluation of membrane fluidity is performed as a separate experiment from the method for detecting binding between the test agent and the lipid bilayer-associated component. The evaluation is performed as a means of quality control, in order to assess whether the artificial supported bilayers are fluid. Thus, the references fail to teach such evaluation *in a method for assaying for an interaction between a test agent and a lipid bilayer-associated component*.

Groves et al. teach evaluation of membrane fluidity in a surface array detector device by fluorescence recovery after photobleaching (FRAP) (see Figure 1 and p. 652, left column, lines 52 to middle column, line 13). Groves et al. further teach that such evaluation established that the membrane fluidity was long-range and that there was no intermixing between different corrals of the device (ibid and p. 651, right column, lines 6-16) and could also be used to determine effective barrier materials (p. 652, middle column, second paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art to include the step of evaluating membrane fluidity by FRAP as taught by Groves et al. in the method of Boxer et al. or Boxer '98 in order to assess range of fluidity and/or measure intermixing between different corrals or expanses in a surface detector array device, such as that of Boxer et al. or Boxer '98. One would have had reasonable expectation of success because Groves et al. teach that their surface detector array devices may be used in methods for assessing interaction with a

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test agent (see p. 653, middle column, paragraph 3 in particular), such as the methods of Boxer et al. and Boxer '98.

Regarding the interpretive “whereby” clause recited in claim 1 (“...whereby the membrane fluidity of at least one of the plurality of lipid bilayer expanses decreases when said test agent binds to said lipid bilayer-associated component”): it is noted that such an interpretive clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps. Therefore, the “whereby” clause is not deemed to further limit the method defined by the claims, and has not been given patentable weight in construing the claims. See *Texas Instruments, Inc. v. International Trade Comm.*, 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) (“A ‘whereby’ clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim.”). See also *Minton v. National Assoc. of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) (“A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.”).

With regard to claim 2, the supported bilayers of Boxer et al. may further comprise receptors including proteins or nucleic acids (column 4, lines 5-11 and column 12, lines 12-15 and 39-42 in particular).

With regard to claims 4-5, Boxer et al. teach that hexa-histidine tags may be attached to the ligands or receptors that are immobilized to the bilayer surface, as well as labels such as avidin or streptavidin that may be coupled to biomolecules to link them to the supported bilayer (column 13, lines 36-59).

With regard to claim 6, Boxer et al. teach a device comprising lipid bilayers doped with the fluorescently labeled lipid probe Texas Red DHPE (column 14, lines 46-47; column 20, lines 15-28; column 21, lines 16-22 and 52-55). The Texas Red label is attached to a lipid bilayer-associated component (phosphatidylcholine) that does not specifically bind to a test agent, i.e., to a background membrane component (see the definition in the specification at p. 7, lines 1-2).

With regard to claims 34-36, examples of test agents include the small molecule acetylcholine (column 18, lines 7-12), proteins (column 4, lines 5-9 and 26-31 and column 5, lines 16-30), and cells (column 18, lines 60-62).

14. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al., or, alternatively, Boxer '98 in view of Groves et al. as applied to claim 1 above, and further in view of Gutschmann et al. ("Interaction of CAP18-Derived Peptides with Membranes Made from Endotoxins or Phospholipids," (2001) Biophysical Journal **80**:2935-2945).

Boxer et al. and Boxer '98 are as discussed above, which fail to teach a method wherein at least one lipid bilayer expanse further comprises a bacterial endotoxin.

Gutschmann et al. teach a method for assaying an interaction between a test agent (CAP18-derived peptides) with bacterial endotoxin (lipopolysaccharide) in differently composed lipid membranes (see the title; abstract; p. 2935, left column, the first paragraph; p. 2395, right column, the first full paragraph; and p. 2936, left column, second paragraph in particular). Gutschmann et al. teach that the reconstituted bilayers that comprise lipopolysaccharide mimic the outer membrane of Gram-negative bacteria (p. 2941, left column, lines 26-30) and such bilayers

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may be employed to assay interaction with the peptides by various biophysical techniques (p. 2941, left column, line 30 to right column, line 3 and the abstract, lines 11-12).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ bilayers comprising lipopolysaccharide, as taught by Gutschmann et al., in the method and device of Boxer et al. (or Boxer '98) and Groves et al., because Gutschmann et al. teach that such bilayers may be successfully employed in order to create a system that mimics the outer membrane of Gram-negative bacteria for use in methods to assay interaction of lipid bilayers with test agents, such as the methods of Boxer et al. and Boxer '98.

15. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al. (US Patent No. 6,228,326; referred to as "Boxer et al."), or, alternatively, Boxer et al. (WO 98/23948; referred to as "Boxer '98") in view of Groves et al. as applied to claim 1 above, and further in view of Salafsky et al. ("Architecture and Function of Membrane Proteins in Planar Supported Bilayers: A Study with Photosynthetic Reaction Centers" *Biochemistry* **1996**, 35:14773-14781).

Boxer et al., Boxer '98, and Groves et al. are as discussed above. Boxer et al. teaches that the lipid bilayer-associated component may comprise a label, such as streptavidin or a His-tag. However, the references fail to teach that the label may be a fluorophore, an electron spin resonance label, a radioactive label, or a nanoparticle.

Salafsky et al. teach attachment of labels, such as biotin and the fluorescent dye rhodamine R-492, to a lipid bilayer-associated component (the protein photosynthetic reaction center (RC)) (see p. 14774-14775, "RC-Biotin and RC-Rhodamine Conjugates of Rb. Sphaeroides RCs" and "Dye Labeling of (M)L189C Rb. Capsulatus RCs"). Labeling with the

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fluorescent dye allowed imaging of the protein in the supported bilayer (p. 14779, "Fluorescence Imaging of Labeled RCs in Supported Bilayers Containing RCs").

Therefore, it would have been obvious to one of ordinary skill in the art to attach a fluorescent dye label to the lipid bilayer-associated component of Boxer et al. (or Boxer '98), as taught by Salafsky et al., in order to allow for the component to be imaged by fluorescence imaging in the method of Boxer et al. (or Boxer '98) and Groves et al. One would have a reasonable expectation of success because Salafsky et al. also teaches lipid bilayer-associated components that are proteins, as in Boxer et al. and Boxer '98.

16. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al. or, alternatively, Boxer '98 in view of Groves as applied to claim 1 above, and further in view of Keinanen et al. (US Patent No. 6,235,535).

Boxer et al., Boxer '98, and Groves et al. are as discussed above, which fail to teach a method wherein the bulk aqueous phase further comprises a second test agent and wherein the method determines whether the second test agent affects the interaction of the test agent with the lipid bilayer-associated component.

Keinanen et al. teach fluorescence-based immunoassay methods for detection of an analyte (the abstract), wherein two lipid-tagged antibody populations are attached to a lipid membrane (one population labeled with a FRET donor fluorophore and one population labeled with a FRET acceptor fluorophore) (column 2, lines 50-60). In one embodiment, planar lipid membranes attached to a solid substrate are used (column 3, lines 4-13). When the lipid-attached antibody contacts a test agent (multivalent antigen), microaggregation occurs due to the free

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lateral mobility of the antibodies, which enables FRET (column 2, line 60 to column 3, line 4). Keinanen et al. also teach indirect immunoassay of a monovalent antigen, wherein a second test agent (monovalent hapten) is added in the presence of the first test agent (Ox16BSA multivalent antigen) (column 3, lines 30-41 and column 10, line 64 to column 11, line 4). Keinanen teach that addition of the second test agent affected the interaction of the first test agent with the lipid-attached antibody, as there was a decrease in the fluorescence changes proportional to the amount of the added second test agent (column 11, lines 4-9).

Therefore, it would have been obvious to one of ordinary skill in the art to include a second test agent, as taught by Keinanen et al., in the bulk aqueous phase comprising the test agent in the method of Boxer et al. (or Boxer '98) and Groves et al. in order to indirectly assay monovalent antigens. One would have reasonable expectation of success because Keinanen et al. also teaches methods involving interaction of test agents with planar lipid membrane-associated components.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-2, 4-7, 10, 34-36, and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-26 of U.S. Patent No. 6,699,719 (Yamazaki et al.) in view of in view of Groves et al.

Although the conflicting claims are not identical, they are not patentably distinct because Yamazaki et al. also claims a method comprising assaying an interaction between a test agent and a lipid-bilayer associated component using a surface detection array device (claim 22). The surface detection array device of Yamazaki et al. also comprises a substrate having a surface defining a plurality of distinct bilayer-compatible surface regions separated by one or more bilayer barrier regions that are formed of different materials, and wherein lipid bilayer expanses are localized above the bilayer-compatible surface regions. The method includes the step of contacting the device with a bulk aqueous phase comprising the test agent.

The claimed method of Yamazaki et al. fails to recite the step of evaluating the membrane fluidity of lipid bilayer expanses.

Groves et al. (discussed above) teaches evaluation of membrane fluidity in a surface array detector device by fluorescence recovery after photobleaching (FRAP) (see Figure 1 and p. 652, left column, lines 52 to middle column, line 13). Groves et al. further teach that such evaluation established that the membrane fluidity was long-range and that there was no intermixing between different corrals of the device (ibid and p. 651, right column, lines 6-16) and could also be used to determine effective barrier materials (p. 652, middle column, second paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art to include the step of evaluating membrane fluidity by FRAP as taught by Groves et al. in the method of

Yamazaki et al. in order to assess range of fluidity and/or measure intermixing between different corrals or expanses of a surface detector array device, such as that of Yamazaki et al.

Response to Arguments

19. The declaration under 37 CFR 1.132 filed 1/20/06 is insufficient to overcome the rejection of claims 1-25, 34-36, and 40 based upon 35 USC 112, first paragraph as set forth in the last Office action because: the declaration has not been considered on the merits because the declaration is unsigned.

20. With regard to the rejection of the claims under 35 USC 112, 1st paragraph as lacking written description, Applicant's arguments have been fully considered but they are not persuasive. Applicant argues (p. 9-12) that one skilled in the art would recognize that the present method is not dependent upon the particular test agent, and that the method is useful regardless of the test agent selected (p. 11, the last paragraph), to which the Examiner disagrees.

The specification discloses that membrane fluidity is decreased in response to binding by the test agent cholera toxin B (CTB) to the lipid bilayer-associated component ganglioside GM1 (see p. 14, line 31 to column 15, line 4; p. 34, line 10 to p. 35, line 13). The specification indicates that the large size and multivalent binding of CTB likely contributes to its reduced mobility when bound to membranes (p. 34, lines 21-23). However, the claims are not restricted to test agents of large size and multivalent binding capabilities, but also include, for example, small molecules, as in claim 34. However, the specification does not disclose examples of small molecules capable of decreasing membrane fluidity upon binding to a surface detector array device. The specification also fails to provide written description of test agents binding to a lipid

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bilayer-associated component that is a bacterial endotoxin, in which the binding results in a decrease of membrane fluidity, as claimed in claim 3. The Examiner maintains that one skilled in the art would not reasonably conclude that the inventors, at the time that the application was filed, had possession of the claimed invention. Applicant further points to the declaration filed under 37 CFR 1.132, which has not been considered on the merits for the reasons discussed above.

21. With regard to the rejection of the claims under 35 USC 112, 1st paragraph (scope of enablement), Applicant's arguments (p. 12-14) have been fully considered but they are not persuasive. Applicant first points to the declaration filed under 37 CFR 1.132, which has not been considered on the merits for the reasons discussed above. Applicant further argues that one skilled in the art would not expect lipid bilayer-associated components to be non-functional, as the prior art teaches PEG "cushions" used to preserve the fluidity (and therefore functionality) of integral membrane proteins (p. 13-14). Applicant points to an article by Wagner and Tamm, which was not supplied as part of an Information Disclosure Statement and has not been considered on the merits since a copy was not made available to the Examiner. Moreover, the argument that one skilled in the art would recognize the applicability of the PEG "cushions" is not found persuasive, since specification does not disclose PEG "cushions". See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

The Examiner maintains that the specification, in disclosing examples in which binding of cholera toxin B (CTB) to the lipid bilayer-associated ganglioside GM1 is detected by

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detecting a decrease in membrane fluidity, fails to reasonably provide enablement for assaying interaction between all possible test agents to lipid bilayer-associated component pairs. As taught in the prior art (see the above rejection) and as noted in the specification (p. 34, lines 21-23), the interaction between CTB and ganglioside GM1 is polyvalent. Moreover, CTB is disclosed to be a large molecule. However, the claims encompass other test agents, including small molecules, and does not stipulate that the test agents be capable of polyvalent binding with the lipid bilayer-associated component. As discussed above, the prior art fails to teach that binding of all test agents is known to affect the membrane fluidity of a supported bilayer; rather, it is known that some small molecules are known not to affect membrane fluidity upon binding to membranes. Moreover, the specification lacks working examples in which test agents other than CTB were shown to affect membrane fluidity upon binding. In light of the prior art teachings, the lack of working examples in which binding of test agents other than CTB can be detected by a decrease in membrane fluidity, the lack of direction/guidance with regard to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope.

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22. With regard to the rejection of claim 36 under 35 USC 112, 2nd paragraph for recitation of the term “cell-vesicle”, Applicant’s arguments (p. 15) have been fully considered but they are not persuasive. Applicant submitted pages of a textbook by Alberts et al. The reference at p. 490 refers to “ghosts”. However, the Examiner did not find the term “cell-vesicle” in the reference and found no indication that this term is well known in the art. The reference by Alberts et al. fails to support Applicant’s position that the term “cell-vesicle” is recognized in the art.

Applicant’s argument that “ghost cells” are synonymous with “cell-vesicles” is not found persuasive because Applicant has also argued that “ghost cells” are synonymous with “phantom cells” (see Applicant’s response, p. 15), yet both “cell-vesicles” and “phantom cells” are recited separately in the claims, which would suggest that the meanings of these terms is not coextensive. Furthermore, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). The rejection is maintained because the term “cell-vesicle” is not defined in the specification, such that one skilled in the art would not be reasonably apprised of the scope of the claimed invention.

23. With regard to the rejection of claim 36 under 35 USC 112, 2nd paragraph for recitation of the relative term “giant” in relation to “vesicles”, Applicant’s arguments have been fully considered but they are not persuasive. Applicant argues that “giant liposomes” is a standard term in the art and is understood to refer to liposomes with a diameter greater than large unilamellar liposomes or about 10 μm or greater. However, such a definition could not be found in the specification.

Applicant submitted an abstract by Riquelme et al. describing the use of “giant liposomes”. However, the examiner notes that the terms “vesicle” and “liposome” are not

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synonymous (see the attached definitions for the terms “vesicle” and “liposome” provided by Dorland’s Illustrated Medical Dictionary (2003) (see attached). Therefore, the reference to “giant liposomes” by Riquelme does not bear on the use of the relative term “giant” in relation to “vesicles”. In addition, the abstract by Riquelme et al. does not include definition of the term “giant liposome” or “giant vesicle”, and does not provide evidence that the term “giant vesicle” refers to liposomes with a diameter greater than large unilamellar liposomes or about 10 μm or greater as argued by Applicant. The rejection is maintained because the term “giant” is a relative term that renders the claim indefinite.

24. With regard to the rejections of claims 1-2, 4-8, 14-15, 19-20, and 34-36 under 35 USC 102(b) as being anticipated by Boxer et al., Applicant’s arguments (p. 16-17) have been fully considered. The rejections have been withdrawn in response to Applicant’s amendments of claim 1 to recite the step of evaluating the fluidity of the lipid bilayer expanse(s). However, the reference has been applied to reject claims 1-7, 10, 34-36, and 40 under 35 USC 103(a) above.

Applicant argues that Boxer et al. fail to teach evaluating binding by evaluation of the membrane fluidity, wherein a decrease in the membrane fluidity indicates that the test agent interacts with the lipid bilayer-associated component (see p. 17, part C., “Analysis”). The Examiner acknowledges that Boxer et al. fails to specifically teach detection of binding by evaluation of membrane fluidity. However, claims are unpatentable over the teaching of the method for assaying an interaction between a test agent and a lipid bilayer-associated component of Boxer et al. and the teaching of evaluation of membrane fluidity by Groves et al. because the claims do not clearly recite a correlation between the step of evaluating membrane fluidity and detection of the interaction between the test agent and the lipid bilayer-associated component

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(see rejection under 112, 2nd paragraph above). As currently recited, the step of evaluating the fluidity is not necessarily related to the detection of the interaction between a test agent and a lipid bilayer-associated component. Therefore, the claims do not exclude detection by SRP or by detection of changes in the transmembrane voltage or current, as taught in Boxer et al.

25. With regard to the rejection of claim 3 as being unpatentable over Boxer et al. in view of Gutsman et al. (now rejected above as unpatentable over Boxer et al. in view of Groves et al., and further in view of Gutsman et al.), Applicant's arguments (p. 19-20) have been fully considered but they are not persuasive. Applicant argues that Boxer et al. fails to teach contacting the device with a test agent that specifically binds to a lipid bilayer-associated component and evaluating the membrane fluidity of one or more lipid bilayer expanses. As discussed above, Boxer et al. and Groves et al. teach such a method. The "whereby" clause recited in amended claim 1 has not been given patentable weight since it has been interpreted as a conclusory or interpretive step that merely states a characterization or conclusion but does not set forth additional active method steps (see rejection under 35 USC 103(a) above).

Applicant further argues that Gutsman et al. fails to teach a method including contacting a membrane with a test agent that binds to the lipid bilayer-associated component, to which the Examiner disagrees. Gutsman et al. teach detection of the interaction between a test agent (CAP18-derived peptide) with a lipid bilayer-associated component (endotoxin or LPS), as discussed above.

Applicant further argues that Gutsman et al. make no mention of evaluating the fluidity of the membrane. However, the Groves et al. reference has been relied upon for this teaching.

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26. With regard to the rejection of claims 9-10 as being unpatentable over Boxer et al. in view of Groves et al., Applicant argues (p. 20-21) that in Boxer et al., the physical properties evaluated are transmembrane voltage and current, which are unique to the protein involved and not to the membrane itself, while in the instant invention, the membrane fluidity decreases upon binding and is then evaluated. This argument is not found persuasive because the claims do not require that the detection of the interaction be by any particular means (i.e. by evaluation of membrane fluidity), and do not exclude detection as in Boxer et al. via transmembrane voltage and current, since claim 1 fails to recite a step in which the interaction between the test agent and the lipid bilayer-associated component is actually detected (see rejection under 112, 2nd paragraph above). Although the claim recites that upon binding, membrane fluidity decreases, and further recites the step of evaluating the fluidity, there is no correlation between evaluation of fluidity and detection of binding recited in the claim. Therefore, the detection of binding by means other than evaluation of fluidity, such as those in Boxer et al., is encompassed by the claims.

Applicant further argues that Boxer et al. and Groves et al. fail to teach that when the test agent is contacted with the lipid bilayer-associated component, the membrane fluidity of at least one of the lipid bilayer expanses is decreased. However, as noted above, the “whereby” clause recited in amended claim 1 (“whereby the membrane fluidity...decreases”) has not been given patentable weight since it has been interpreted as a conclusory or interpretive step since it does not set forth any additional active method steps, but rather states a characterization or conclusion of the results of the method steps previously recited in the claims (see rejection under 35 USC 103(a) above). The specification also indicates that the reduction in membrane fluidity is a

consequence of the interaction between CTB and ganglioside GM1 (p. 14, line 33 to p. 15, line 2) and does not indicate that any additional steps would be required in order to reduce membrane fluidity.

27. With regard to the rejection of claim 40 as being unpatentable over Boxer et al. in view of Keinanen (claim 40 is rejected under 35 USC 103 above as being unpatentable over Boxer et al. in view of Groves et al, and further in view of Keinanen)), Applicant argues (p. 21) as above that Boxer et al. teaches evaluating transmembrane voltage and current, which are unique to the protein involved and not the membrane itself. This argument is not found persuasive for the reasons discussed above. Applicant further argues that Boxer et al. fails to teach evaluating fluidity with respect to evaluating binding of a test agent. However, the Groves et al. reference has been relied upon for the teaching of evaluation of fluidity.

28. With regard to the rejection of claims 1-25, 34-36, and 40 under the judicially-created doctrine of obviousness-type double patenting, Applicant argues that US 6,699,719 fails to teach evaluation of membrane fluidity in order to assay the interaction of the test agent and the lipid bilayer associated component (p. 23). Claims 1-2, 4-7, 10, 34-36, and 40 have been rejected under this statute above as being obvious over US 6,699,719 in view of Groves et al. Applicant's arguments are not persuasive because as noted above, the instant claims do not correlate the evaluation of membrane fluidity with the detection of the interaction. Although US 6,699,719 does not recite the step of evaluating the fluidity of the bilayer expanse(s), such a teaching is found in Groves et al.

Conclusion

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29. No claims are allowed.

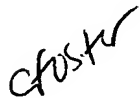
30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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